

WEST

L24: Entry 10 of 19

File: USPT

Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700781 A

TITLE: Method for treating Kaposi's sarcoma and HIV infections

APD:

19941110

BSPR:

Human chorionic gonadotropin (HCG) is a polypeptide produced by the human placenta and is composed of .alpha. and .beta. subunits. The e chain of HCG is homologous with leutinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH); the .beta. subunit is closest in structure to the .beta. subunit of LH, however HCG acts biologically most like LH but with some FSH properties.

BSPR:

Scientifically elegant observations of the presence of HCG receptors on Kaposi's sarcoma cells as well as other elegant observations of the interplay of human reproductive endocrinology and Kaposi's sarcoma have emerged over the last two years. In the Sep. 1993 issue of Treatment Science, two pregnant women were noted to have "spontaneous resolution", of Kaposi's sarcoma. Dr. Robert Gallo, Chief of the Laboratory of Tumor Cell Biology of the National Cancer Institute, reported on Aug. 8, 1994 in Yokohama, Japan, that administration of HCG to nude mice infected with a tumor cell line derived from human Kaposi's sarcoma eradicated all evidence of this tumor in this murine model. Dr. Gallo et al. also noted that they were unable to grow this tumor cell line in a female mouse during the first trimester of the pregnancy. Administration of HCG in the range of 5-10 International Units (IU) per gram of mouse weight three times per week intramuscularly resulted in the regression of Kaposi's sarcoma in nude mice. See Japan Science Scan, Aug. 15, 1994.

BSPR:

Much of human reproductive function is controlled by the family of heterodimeric human glycoprotein hormones identified above. HCG itself is a water-soluble glycoprotein derived from human pregnancy urine. It is prepared for intramuscular injection as a sterile lyophilized powder. HCG is marketed by, e.g., Serono in vials containing either 5,000 or 10,000 USP Units.

BSPR:

During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle and the mid-cycle LH surge triggers ovulation. HCG can substitute for

LH in this function. During a normal pregnancy, HCG secreted by the placenta maintains the corpus luteum after LH secretion decreases, supporting continued secretion of estrogen and progesterone in preventing menstruation.

BSPR:

HCG also is present in certain tumors. For example, germ cell tumors have high levels of HCG. Other tumors, such as adenocarcinoma of the lung and pancreatic adenocarcinoma, also contain high HCG levels.

BSPR:

The interplay of various hormones in the context of treating Kaposi's sarcoma itself specifically is unclear. For example, notwithstanding the stimulation of androgens in males treated with HCG. Rosenthal, E. et al. (Revue Medicale Interne (1994) 15:186-189) reported that a 59-year-old bisexual man without HIV-1 or HIV-2 infection developed AIDS-related-like Kaposi's sarcoma while the patient was receiving both androgen and steroid therapy for aplastic anemia. The lesions regressed after interruption of therapy, despite the persistence of aplastic anemia.

BSPR:

In accomplishing these and other objects, there has been provided, in accordance with one aspect of the present invention, a method for counteracting HIV in an individual infected with HIV or at risk from HIV infection, comprising the step of administering human chorionic gonadotropin (HCG) to the individual. In a preferred embodiment, the individual receives said HCG such that the individual has a blood level of HCG ranging between about 10,000 and about 300,000 IU per liter of blood.

BSPR:

According to another aspect of the present invention, a method is provided for treating Kaposi's sarcoma in an individual who has a Kaposi's tumor, comprising the administration of human chorionic gonadotropin (HCG) to the individual. Pursuant to a preferred embodiment, the individual receives an administration of 5,000 and 10,000 IU of HCG per kilogram of body weight, said administration being repeated three times per week.

BSPR:

I have observed in my clinical practice that none of the patients with Kaposi's sarcoma have high serum levels of HCG. In contrast, I have observed that all patients with Kaposi's sarcoma have low serum levels of HCG. Through detailed observations of the immunoendocrine aspects of HIV infections, I surmised that administration of high doses of HCG would usefully treat Kaposi's sarcoma.

BSPR:

Thus, as a result of protocols beginning with doses of HCG at levels described below for the treatment of hypogonadotropic hypogonadism, and increasing these dosages substantially, my patients have experienced a rapid improvement in overall health

and a regression of the Kaposi's sarcoma lesions. In addition, one patient with limited cutaneous Kaposi's was treated with moderate dose, intramuscular HCG, causing near total regression of the Kaposi's tumor. He was lost to follow up for several days and returned with massive new lesions, as well as an exacerbation of those that had been in near remission. With renewed treatment according to the present invention, all lesions regressed and no new lesions formed.

BSPR:

Furthermore, two patients who did not respond effectively to irradiation and chemotherapy, respectively, were treated with intramuscular HCG. The result in both cases was a regression of lesions.

BSPR:

As a rationale for these observations, it is noted that HCG receptors on the corpus luteum are activated by placental HCG. This in turn causes continued progesterone (and estrogen) secretion from the corpus luteum which directly (or perhaps indirectly, via HCG) allows endometrial vascular structural changes, i.e., decidual changes, to favor a normal pregnancy. In the same fashion, HCG receptors on Kaposi's Sarcoma cells are activated by exogenous HCG, which in turn allows normalization of vascular tissue in these vascular anaplastic cells. In essence, therefore, placental HCG changes endometrial vascular structure to provide a bed for normal fetal development, while exogenous HCG changes Kaposi's sarcoma cells from anaplastic (or dysplastic) to normal.

BSPR:

I have administered HCG to my patients that is marketed commercially by Serono, Inc., under the brand name PROFASI.RTM.. It also is marketed by Wyeth Ayerst, under the name PREGNYL, and there are other commercial sources for suitable HCG formulations.

BSPR:

Contraindications for HCG are precocious puberty, prostatic carcinoma or other androgen-dependent neoplasms and a prior allergic reaction to HCG. Adverse reactions include headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, pain at the site of injection as well as various hypersensitivity reactions. Administration of HCG according to the present invention should take into account these considerations.

BSPR:

I contemplate the administration of HCG, for an average patient of about 65 kg, in an amount of about 325,000 to about 650,000 IU/dose when HCG is administered three times per week. The administration of lower doses of HCG may be effective as well, but what is important is that the administration of HCG will cure Kaposi's sarcoma lesions and prevent the occurrence of additional lesions. Appropriate dosages for individual patients can be developed readily by those skilled in the art according to overall health indicators.

DEPR:

The following examples describe the clinical improvements of four HIV-infected patients with Kaposi's sarcoma treated in my practice. These examples are not intended to limit the scope of the invention in any way. For example, -it is contemplated that recombinant HCG or active fragments of HCG will provide the anti-Kaposi's sarcoma activity of the molecule isolated from human urine.

DEPR:

Patient KB was a 30 year old white male, diagnosed as having Kaposi's sarcoma about 10 months prior to the initiation of HCG therapy. Within three months the patient was placed on chemotherapy and received dosages approximately every three weeks for about five months. Combination chemotherapy was administered, specifically bleomycin, adriamycin (doxorubicin), and vincristine according to the standard 1987 protocol known to physicians who treat Kaposi's sarcoma. The therapy caused depression and myelosuppression. It resulted in minimal regression of existing lesions, but new lesions also appeared. Before the start of HCG therapy, Patient KB developed lesions on the back, face, neck and arms that were not present at beginning of chemotherapy.

DEPR:

The following dosages of HCG were administered IM according to the standard protocols for administration of this therapeutic on the following schedule: 1,000 IU (Day 1), 5,000 IU (Day 2), 8,000 IU (Day 3), 14,000 IU (Day 4), 20,000 IU (Day 5), 24,000 IU (Day 6), 30,000 IU (Day 7), 30,000 IU (Day 8), 50,000 IU (Day 9), 60,000 IU (Day 11), 70,000 IU (Day 12), 80,000 IU (Day 13), 90,000 IU (Day 14), 100,000 IU (Day 15), 150,000 IU (Day 18) and 162,000 IU (Day 19).

DEPR:

The following dosages of HCG were administered IM according to the standard protocols for administration of this therapeutic on the following schedule: 5,000 IU (Day 1), 10,000 IU (Day 2), 20,000 IU (Day 3), 30,000 IU (Day 4), 40,000 IU (Day 5), 60,000 IU (Day 8), 80,000 IU (Day 9), and 120,000 IU (Day 14).

DEPR:

Patient BW is a 39 year old white male, diagnosed as being HIV positive about eight years prior to receiving HCG therapy for Kaposi's sarcoma. About 30 months prior to receiving HCG therapy, Patient BW was treated with chemotherapy for Kaposi's sarcoma lesions on his legs. Chemotherapy was restarted about six months later and continued for about two months. The patient received combined chemotherapy for about the nine months preceding initiation of HCG therapy. His lesions were generally flat in profile. Chemotherapy appeared to prevent spread of the lesions, but did not appear to cause them to regress. About one month before HCG therapy, this patient began to experience nausea, vomiting, depression and hair loss, and developed stomatitis. He also had hypogonadotropic hypogonadism.

DEPR:

The following dosages of HCG were administered IM according to the standard protocols for administration of this therapeutic on the following schedule: 1,000 IU (Day 1), 1,000 IU (Day 3), 5,000 IU (Day 7), 7,500 IU (Day 8), 9,000 IU (Day 9), 9,000 IU (Day 10), 13,000 IU (Day 11), 17,000 IU (Day 12), 20,000 IU (Day 14), 20,000 IU (Day 15), 20,000 IU (Day 16), 22,000 IU (Day 17), 24,000 IU (Day 18), 28,000 IU (Day 22), 30,000 IU (Day 23), 30,000 IU (Day 24), 40,000 IU (Day 26), 50,000 IU (Day 28), 60,000 IU (Day 29), 80,000 IU (Day 31), 90,000 IU (Day 32), 50,000 IU (Day 33), 120,000 IU (Day 35), 150,000 IU (Day 37), 180,000 IU (Day 39) and 200,000 IU (Day 42).

DEPR:

Patient LM is a 44 year old white male with AIDS. About eight months prior to beginning HCG therapy, this patient presented with a 1.times.1.5 cm area of redness on the right anterior neck. One month later, this area had changed into a 2.times.1 cm red plaque with some nodularity. After local radiation treatment, the lesion regrew. The patient also had developed hypogonadotropic hypogonadism by the time that HCG therapy was commenced.

DEPR:

The following dosages of HCG were administered IM according to the standard protocols for administration of this therapeutic on the following schedule: 5,000 IU (Day 1), 10,000 IU (Day 2), 20,000 IU (Day 3), 30,000 IU (Day 4), 40,000 IU (Day 5), 25,000 IU (Day 6), 60,000 IU (Day 8) and 80,000 IU (Day 9).

DEPR:

The foregoing examples present clinical findings of several AIDS patients who have been treated with elevated dosages of HCG in connection with therapy for Kaposi's sarcoma. The present invention is not limited, however, to AIDS-related Kaposi's sarcoma, but rather can be used generally to treat the cancer. In this regard I contemplate that an optimum treatment schedule would be to administer HCG about three times per week, as discussed above.

DEPR:

In appropriate formulations that are known and conventional to those skilled in the art, the administration of HCG by various routes of administration is contemplated, including intramuscular, oral, subcutaneous, transmucosal, transdermal and parenteral. Administration of HCG specifically is contemplated through a timed-release drug delivery system, e.g., transdermal skin patches, such as are well-known to physicians and those skilled in the relevant art. Exemplary devices (not to be considered limitative of the present invention) are disclosed, e.g., in U.S. Pat. Nos. 5,316,759, 5,324,521, 5,326,570, 5,332,577, 5,336,213, 5,336,505, 5,344,656, 5,346,701 and 5,350,581.

DEPR:

According to another embodiment of the present invention, HCG is given at an appropriate dose through an effective delivery system to prevent transmission of HIV and to kill HIV in individuals

already infected. While the invention is not limited by the mechanism(s) underlying effectiveness in this regard, it is believed that HCG administered according to the present invention inhibits reverse transcriptase or alters thymic function.

DEPR:

More specifically, it has been discovered that HCG inhibits HIV infection, via immune mechanisms such as occupying receptors on the thymus or via inhibition of viral reverse transcriptase. This explains why pregnant women who produce very high levels of HCG in their first trimester of pregnancy do not transmit HIV to their fetuses during this time period. HCG-mediated reversal of HIV-positive, maternal lymphocytes and monocytes to negatives prevents transmission of HIV infected cells to the fetus. After the normal LH surge and LH decline in the mother, placental HCG is produced, maintaining corpus luteum secretory activity and allowing appropriate vascularization (decidual changes) in the endometrium to maintain pregnancy.

DEPR:

Accordingly, "appropriate dose" in the context of the present invention is guided by the observation that AIDS never occurs during the first trimester of pregnancy, and only rarely during the second and third trimesters. Blood levels of HCG between 10,000 and 300,000 IU per liter of blood are typically seen in a mother's blood during the first three months of gestation, falling to 20,000 to 40,000 IU during the last six months of gestation. At parturition and the delivery of a placenta, there is a massive decline in HCG, and baby is rendered at risk to acquire HIV.

DEPR:

Illuminated by this understanding, the present contemplates HCG administration to HIV-infected individuals, or to individuals at risk to develop AIDS, such that blood levels are maintained at 10,000 to 300,000 IU per liter of blood, more preferably on the order of 100,000 IU per liter of blood, i.e., in the same range of maternal HCG levels during the first trimester of pregnancy. To achieve such levels according to the present invention, HCG can be administered intramuscularly but not without the technical difficulties associated with multiple injections. More preferred approaches to this end include a transdermal HCG patch and an implantable HCG delivery system, for example, a device such as NORPLANT.RTM..

DEPR:

A bioavailable, sustained-release oral formulation of HCG also is possible. In addition, recombinant HCG should be feasible for human administration in this regard, allowing for an HCG-containing product that is purer, more concentrated and easier to administer.

CLPR:

1. A method of treating an individual infected with HIV comprising the step of administering an amount of human chorionic gonadotropin (HCG) such that said individual has a blood level of HCG of at least 10,000 IU per liter of blood is attained.

CLPR:

2. A method for treating Kaposi's sarcoma in an individual, comprising the administration of human chorionic gonadotropin (HCG).

CLPR:

3. A method according to claim 2, wherein said individual is administered a dosage of HCG comprising at least 5,000 IU per kilogram of body weight, said dosage being administered to said individual at least three times a week.

ORPL:

Bourinbaiar et al. "Inhibitory Effect of Human Chorionic Gonadotropin (HCG) on HIV-1 Transmission from Lymphocytes to Trophoblasts," FEBS LETS., 309:82, 1992.

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USPT	l3 and @pd<19960313	4	<u>L4</u>
USPT	l1 or l2	14	<u>L3</u>
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USPT	l35 and kDa	0	<u>L37</u>
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USPT	5589579[pn] or 5773579[pn] or 4990454[pn] or 4892935[pn]	4	<u>L35</u>
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JPAB,EPAB,DWPI	ka-93	0	<u>L28</u>
JPAB,EPAB,DWPI	ka93	0	<u>L27</u>
USPT	ka93	0	<u>L26</u>
USPT	ka-93	2	<u>L25</u>
USPT	l23 and @ad<19960313	19	<u>L24</u>
USPT	l2 and (HCG or (beta-HCG) or (HCG-beta) or (chorionic gonadotrophin) or (alpha fetoprotein) or AFP or (tissue polypeptide antigen))	33	<u>L23</u>
USPT	l21 and @ad<19960313	19	<u>L22</u>
USPT	l18 with glycoprotein	22	<u>L21</u>
USPT	l18 same glycoprotein	35	<u>L20</u>
USPT	l18 and glycoprotein	129	<u>L19</u>
USPT	l17 with ((B or beta) adj subunit)	238	<u>L18</u>
USPT	HCG or (chorionic gonadotropin)	2610	<u>L17</u>
USPT	l14 and l15	11	<u>L16</u>
USPT	antigen with (secretion or secrete or secreted or shed or shedding or release or released)	3600	<u>L15</u>
USPT	l2 with antigen	28	<u>L14</u>
USPT	l2 with ((sero or serum or tumor or tumour) adj marker)	0	<u>L13</u>
USPT	l1 with l2	5	<u>L12</u>
JPAB,EPAB,DWPI	l10 and glycoprotein	3	<u>L11</u>
JPAB,EPAB,DWPI	lung adj2 adenocarcinoma	94	<u>L10</u>
USPT	l8 and ((sero or serum or tumor or tumour) adj marker)	20	<u>L9</u>
USPT	l2 and (secretion or secrete or secreted or shed or shedding or release or released)	233	<u>L8</u>
USPT	l6 with l2	1	<u>L7</u>
USPT	l1 with (secretion or secrete or secreted or shed or shedding or release or released)	763	<u>L6</u>
USPT	l3 same l2	0	<u>L5</u>
USPT	l3 with l2	0	<u>L4</u>
USPT	l1 adj3 (secretion or secrete or secreted or shed or shedding or release or released)	196	<u>L3</u>
USPT	lung adj2 adenocarcinoma	407	<u>L2</u>
USPT	glycoprotein	10905	<u>L1</u>

WEST

L9: Entry 18 of 20

File: USPT

Feb 5, 1991

DOCUMENT-IDENTIFIER: US 4990454 A

TITLE: YH206 cell line and monoclonal antibody produced by it

BSPR:

The monoclonal antibody 19-9 as ascertained by Koprowski et al. can recognize a blood group-related antigen (Somatic Cell Genetics, 3, 952-972 (1979)) and is used clinically for detection of a novel tumor marker. However, this antibody is positive not only to pancreas cancer and stomach cancer but also to colon cancer (59%). Among lung cancers, it is reactive to squamous epithelium carcinoma (3 cases in 4 cases) and small cell carcinoma (4 cases in 9 cases) in addition to adenocarcinoma. Thus, it is not specific to adenocarcinoma.

BSPR:

As a result of extensive study, there has now been successfully obtained a monoclonal antibody which is specifically reactive to adenocarcinoma such as lung adenocarcinoma, stomach adenocarcinoma and pancreas adenocarcinoma and hardly reactive to non-adenocarcinoma such as squamous epithelium carcinoma, large cell carcinoma and small cell carcinoma as well as normal cells. It has also been found that the diagnosis of various adenocarcinoma can be successfully carried out by immuno-chemical measurement of the specific antigen leaked out into the blood with said antibody.

BSPR:

According to the present invention, there is provided a monoclonal antibody having a specific reactivity to human adenocarcinoma cells, said antibody being produced from hybridoma cells obtainable by cell fusion of myeloma cells and mammalian animal cells immunized with human adenocarcinoma cells. Quite surprisingly, the specific antigen corresponding to said antibody leaks out into the blood from various adenocarcinoma cells. It is therefore possible to make the diagnosis of various cancers by immuno-chemical measurement of the specific antigen in the blood with said antibody. Further, said antibody is characteristic in reacting specifically with human adenocarcinoma cells and can, for instance, react with human lung cancer cells, especially lung adenocarcinoma. The antibody is thus useful for distinguishing various lung cancers. Furthermore, the blood level of the antigen corresponding to said antibody increases with the progress of the symptomatic stage of lung cancer so that the antibody can be used for investigation of the progressive degree of the cancer.

BSPR:

The antibody-producing cells can be obtained by immunizing mammalian animal cells with human lung adenocarcinoma cells as the antigen. The human lung adenocarcinoma cells are not limitative, and any cultured human lung adenocarcinoma cells as already ascertained may be used. Especially preferred are human lung adenocarcinoma A549 cells. The mammalian animal cells are also not limitative, and their selection may be made appropriately taking into consideration their adaptability with myeloma cells used for cell fusion. In general, murine cells are used for this purpose. Immunization may be carried out by a per se conventional procedure. For instance, human cancer cells are diluted with a physiological saline solution and optionally admixed with Freund's complete adjuvant to make a suspension, which is administered intracutaneously into animals. Administration is effected several times at appropriate intervals. On day 3 or 4 after the last administration, animals having a high antibody titer are chosen, and the spleen cells are taken out for the use as the immuno-competent cells, i.e. antibody-forming or antibody-producing cells.

BSPR:

The immuno-histological diagnosis with the monoclonal antibody YH206 and the diagnosis of cancer by measurement of the corresponding specific antigen (tumor marker) in the body fluid will be hereinafter explained.

DEPR:

Into each of BALB/c mice, human lung adenocarcinoma A549 cells (1.times.10.sup.7) were intraperitoneally administered 4 times with intervals of 2 weeks. On the third day after the last immunization, the spleen was taken out. Spleen cells (1.times.10.sup.8) and murine myeloma X63-Ag8.653 cells (1.times.10.sup.7) were subjected to cell fusion by the use of polyethyleneglycol (molecular weight, 1500) as the fusion promoting agent. The above cells were cultivated in a HAT culture medium (RPMI 1640 culture medium containing hypoxanthine, aminopterin, thymidine and 10% fetal calf serum) in a culture plate of 96 holes. After 1 week, the HAT culture medium was exchanged with a fresh one (50 .mu.l) once every 3 days. After 2 to 3 weeks, 280 clones were observed in 400 wells. Screening was carried out using the supernatants from these 280 wells.

DEPR:

Screening was effected by application of the indirect immuno-fluorescent antibody method and the indirect immuno-peroxidase method. The former method was performed by the use of the hybridoma supernatant as the primary antibody and the FITC labeled rabbit anti-mouse immuno-globulin as the secondary antibody, and the reactivity with human lung adenocarcinoma A549 was investigated by the aid of a fluorescent microscope. Among the hybridoma cells associated with human lung adenocarcinoma A549 cells as used in immunization, the hybridoma YH206 cells strongly reactive to lung adenocarcinoma on a tissue slice were chosen and subjected to cloning twice.

DEPR:

The latter method was performed by fixing the tissue materials

obtained from various cancers and fetal tissues with 10% formalin, embedding the fixed specimens in paraffin, selecting lung adenocarcinoma, lung alveolar cell carcinoma, lung epidermoid carcinoma and lung large cell carcinoma and normal lung from the embedded specimens and examining their reactivity according to the Watanabe et al. method ("Enzyme Antibody Method, Theory-Operation, Explanation and its Application", pages 33-39 (1984)).

DEPR:

In the case of lung cancers, a relatively limited reactivity to adenocarcinoma and alveolar cell carcinoma was indicated, and 11 cases were positive in 15 cancers. The staining pattern of the adenocarcinoma was a labeling of the apical surface of tumor cell, while that of the lung epidermoid carcinoma was cytoplasmic. In the case of large cell carcinoma, staining property was recognized in one of 5 cases, but its observation was limited to a part of cancer cells. In the case of small cell carcinoma, no positive reaction was observed. In the case of other organ carcinomas, positive reaction was observed in 3 cases of 4 pancreas cancers, 6 cases of 9 stomach cancers and 1 case of 1 gall bladder cancer. In stomach adenocarcinoma, most cases were positive in an apical surface and also in secreted products with a tendency that mucin lake is strongly stained. On the other hand, stomach signet-ring cell carcinoma (0/3), liver hepatocellular carcinoma (0/2), large intestine carcinoma (0/10), kidney cancer (0/1), breast cancer (0/2) and gall bladder adenocarcinoma (0/1) gave no reactivity.

DEPR:

It was investigated whether the decrease or disappearance of the antigen determinant is caused by treatment with a protease such as trypsin or protease V 8. Namely, cultured cells (2.times.10.sup.6) of lung adenocarcinoma A549 were suspended in an RPMI 1640 culture medium (1 ml) and reacted with any enzyme solution (1 ml) as hereinafter mentioned at 37.degree. C. for 1 hour. Then, a 10% FCS added RPMI 1640 culture medium (8 ml) was added thereto to stop the reaction, washed well with RPMI and subjected to observation on the reactivity with the monoclonal antibody according to the indirect immunofluorescent antibody method. As said enzyme solution, there were used the ones chosen from the following five kinds: neuraminidase F (Seikagaku Kogyo) (0.1 .mu./ml), protease V 8 (Miles) (0.5 mg/ml), trypsin (Warsinton) (0.5 mg/ml), glycosidase (mixed) (Seikagaku Kogyo) (2 mg/ml) and endoglycosidase H (Seikagaku Kogyo) (0.1 .mu./ml). No decrease or disappearance of the antigen determinant was observed by treatment with any of the above five kinds of enzymes. This fact supports that the antigen determinant may be a sugar chain.

DEPR:

Detection and immunochemical investigation of the corresponding antigen in the lung adenocarcinoma supernatant:

DEPR:

Human lung adenocarcinoma cell line A549 and hybridoma YH206 have been deposited under the terms of the Budapest Treaty with the Fermentation Research Institute, Agency of Industrial Science and

Technology, Ibaragi-ken, Japan and have respectively assigned Accession Numbers FERM BP-2000 and FERM BP-2001.

DETL:

property	Tissue	
	Lung	
adenocarcinoma	++ (*) (9/13) (**)	alveolar cell carcinoma ++ (2/2)
epidermoid carcinoma	F+ (1/6)	large cell carcinoma F+ (1/5)
small cell carcinoma	- (0/6)	Pancreas adenocarcinoma ++ (3/4)
adenocarcinoma	+ (6/9)	Stomach singnet-ring cell carcinoma - (0/3)
cholangiocarcinoma	+ (1/1)	Liver hepatocellular carcinoma - (0/2)
Breast scirrhous carcinoma	- (0/2)	Colon adenocarcinoma - (0/10)
Kidney Grawitz's tumor	- (0/1)	Gall bladder adenocarcinoma - (0/1)

(*) Staining intensity: ++, strongly positive; +, positive; F+, faintly positive; -, negative. (**) Number of positive/number of tested.

ORPL:

Endo, T. et al., "Preparation of a Monoclonal Antibody to Human Lung Adenocarcinoma Cells and Detection of Corresponding Antigen(s) in Sera of Malignant Diseases", Sapporo Med. J., vol. 54, No. 4, pp. 393-410, Oct., 1985.

ORPL:

Vark, N. M. et al., "Antigens Associated with a Human Lung Adenocarcinoma Defined by Monoclonal Antibodies", Cancer Research, vol. 44, pp. 681-687, Feb., 1984.

ORPL:

Zimmer, A. M. et al., (I) "Radioimmunoscintigraphy of Human Lung Adenocarcinoma with Iodine-131 Tumor-Specific Monoclonal Antibody", 4th Annual Congress for Hybridoma Research, San Francisco, Calif., U.S.A., Feb. 3-6, 1985, Hybridoma, vol. 4, No. 1, p. 72, 1985.

ORPL:

Zimmer, A. M. et al. (II), "Radioimmunoscintigraphy of Human Lung Adenocarcinoma with ¹³¹I Tumor-Specific Monoclonal Antibody", 30th Annual Meeting of the Society of Nuclear Medicine (Central Chapter), Chicago, Ill., U.S.A., Mar. 21-23, 1985. J. Nucl. Med., vol. 26, No. 6, p. 675, 1985.

ORPL:

Endo, T. et al., Report of General Meeting of Japan Immunological Association, vol. 14, 123 (P. 572), "Preparation of Monoclonal Antibody to Human Lung Adenocarcinoma Cells", (Nov. 10, 1984).

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USPT	l1 and l2	110	L54
USPT	152 and (MW\$1 or (molecular weight))	4	L53
USPT	l1 same l2	6	L52
USPT	KA93	0	L51
USPT	149 adj5 (MW\$1 or (molecular weight))	0	L50
USPT	tissue polypeptide antigen	32	L49
USPT	147 adj5 (MW\$1 or (molecular weight))	13	L48
USPT	(alpha fetoprotein) or AFP	1883	L47
USPT	143 adj5 (MW\$1 or (molecular weight))	27	L46
USPT	143 with (MW\$1 or (molecular weight))	69	L45
USPT	143 same (MW\$1 or (molecular weight))	184	L44

USPT	(HCG or (beta-HCG) or (HCG-beta) or (chorionic gonadotrophin))	1979	<u>L43</u>
USPT	ks1/4Mab	0	<u>L42</u>
USPT	ks1 with glycoprotein	0	<u>L41</u>
USPT	ks1	264	<u>L40</u>
USPT	l35 and glycoprotein	2	<u>L39</u>
USPT	l35 and (MW or MW\$1 or (molecular weight))	1	<u>L38</u>
USPT	l35 and kDa	0	<u>L37</u>
USPT	l35 and kD	0	<u>L36</u>
USPT	5589579[pn] or 5773579[pn] or 4990454[pn] or 4892935[pn]	4	<u>L35</u>
USPT	KA-93	2	<u>L34</u>
USPT	6015680[pn]	1	<u>L33</u>
PGPB	6015680[pn]	0	<u>L32</u>
PGPB	5589579[pn]	0	<u>L31</u>
PGPB	5589579[pn] or 5773579[pn] or 4990454[pn] or 4892935[pn]	0	<u>L30</u>
PGPB	ka-93	0	<u>L29</u>
JPAB,EPAB,DWPI	ka-93	0	<u>L28</u>
JPAB,EPAB,DWPI	ka93	0	<u>L27</u>
USPT	ka93	0	<u>L26</u>
USPT	ka-93	2	<u>L25</u>
USPT	l23 and @ad<19960313	19	<u>L24</u>
USPT	l2 and (HCG or (beta-HCG) or (HCG-beta) or (chorionic gonadotrophin) or (alpha fetoprotein) or AFP or (tissue polypeptide antigen))	33	<u>L23</u>
USPT	l21 and @ad<19960313	19	<u>L22</u>
USPT	l18 with glycoprotein	22	<u>L21</u>
USPT	l18 same glycoprotein	35	<u>L20</u>
USPT	l18 and glycoprotein	129	<u>L19</u>
USPT	l17 with ((B or beta) adj subunit)	238	<u>L18</u>
USPT	HCG or (chorionic gonadotropin)	2610	<u>L17</u>
USPT	l14 and l15	11	<u>L16</u>
USPT	antigen with (secretion or secrete or secreted or shed or shedding or release or released)	3600	<u>L15</u>
USPT	l2 with antigen	28	<u>L14</u>
USPT	l2 with ((sero or serum or tumor or tumour) adj marker)	0	<u>L13</u>
USPT	l1 with l2	5	<u>L12</u>
JPAB,EPAB,DWPI	l10 and glycoprotein	3	<u>L11</u>

JPAB,EPAB,DWPI	lung adj2 adenocarcinoma	94	<u>L10</u>
USPT	l8 and ((sero or serum or tumor or tumour) adj marker)	20	<u>L9</u>
USPT	l2 and (secretion or secrete or secreted or shed or shedding or release or released)	233	<u>L8</u>
USPT	l6 with l2	1	<u>L7</u>
USPT	l1 with (secretion or secrete or secreted or shed or shedding or release or released)	763	<u>L6</u>
USPT	l3 same l2	0	<u>L5</u>
USPT	l3 with l2	0	<u>L4</u>
USPT	l1 adj3 (secretion or secrete or secreted or shed or shedding or release or released)	196	<u>L3</u>
USPT	lung adj2 adenocarcinoma	407	<u>L2</u>
USPT	glycoprotein	10905	<u>L1</u>

(FILE 'HOME' ENTERED AT 18:12:46 ON 17 MAY 2001)

FILE 'MEDLINE, BIOSIS' ENTERED AT 18:12:55 ON 17 MAY 2001

L1 6 S (1993 AND 216 AND 97)/SO
L2 6 DUP REM L1 (0 DUPLICATES REMOVED)
L3 28440 S (CHORIONIC GONADOTROPHIN) OR HCG
L4 3093 S L3 AND ((B OR BETA) (A) SUBUNIT)
L5 0 S L4 AND GLYCOPORTEIN
L6 1489 S L3 AND GLYCOPROTEIN
L7 2 S L3 (W) GLYCOPROTEIN
L8 1 DUP REM L7 (1 DUPLICATE REMOVED)
L9 62883 S LDH OR (LACTATE DEHYDROGENASE)
L10 60517 S L9 NOT CYTOCHROME
L11 265 S L9 (S) GLYCOPROTEIN
L12 262 S L11 NOT CYTOCHROME
L13 53 S L12 AND (TUMOR OR TUMOUR OR CANCER)
L14 32 DUP REM L13 (21 DUPLICATES REMOVED)
L15 24057 S TPA OR (TISSUE POLYPEPTIDE ANTIGEN)
L16 383 S L15 (S) (GLYCOPROTEIN)
L17 1562 S TISSUE POLYPEPTIDE ANTIGEN
L18 26 S L17 (S) GLYCOPROTEIN
L19 18 DUP REM L18 (8 DUPLICATES REMOVED)
L20 3 S L19 AND LUNG
L21 2 S L19 AND PULMONARY
L22 3 S L21 OR L20

4/7/31 352
Mab IM+1